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Case report

Cystic fibrosis: presentation with other diseases, the experience in Saudi Arabia

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Abstract

Simultaneous occurrence of Cystic fibrosis and other inherited diseases or congenital anomalies has been rare. This association has never been described before in the Arab population. In this report we describe the first report on cystic fibrosis in association with other diseases in the same patient such as sickle cell disease, Insulin dependant Diabetes mellitus, congenital adrenal hyperplasia, cardiac anomalies in twins and Ehler's Danlos syndrome. We also evaluate their effects on CF patients and review the literature in this aspect.

Keywords: Cystic fibrosis; Arab; Inherited diseases; Congenital anomalies

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disease. It is the most common hereditary disease in Caucasian populations, with an incidence in the US of 1 in 4100 live births and an estimated gene frequency of 3% [1]. The incidence of CF in Saudi Arabia has been estimated to be 1:4243 live births [2].

Few reports have described the association of CF with SyringoMyelia and scoliosis [3]; another described Lymphoblastic leukemia [4], Gastro-intestinal cancer [5], intra sylvian fibroma [6], congenital generalized hamartoma [7], and infantile hypertrophic pyloric stenosis [8] in association with cystic fibrosis. Most of the diseases mentioned earlier have affected the prognosis of CF course in most of the patients.

In this report we describe our experience as the only referral center in Saudi Arabia for CF patients in this subject and compare our experience with that mentioned in the literature for the same association.

2. Material and method

A retrospective review of medical records of all confirmed cases with CF based on high sweat chloride test and or identification of Cystic fibrosis Transmembrane regulator gene mutations (CFTR) during the period Nov. 1994–Oct. 2002 [9,10]. Demographic, clinical and prognostic data are presented and compared with similar cases in the literature.

3. Results

A total of 190 CF patients were diagnosed during an 8 year period. One hundred and sixty-four (86%) patients are alive, 26 (14%) died. Ninety-nine (52%) were males and 91 (48%) were females. Age at diagnosis 2.88 ± 3.5 years, and period of follow up 3 ± 3 years. Mean survival of 11 years [10]. Eighty-eight percent of the families were of consaquinous marriage (Consanguinity is 50% in the general population) [10]. The following are the different diseases presented simultaneously within the same patients with CF

4. CF and sickle cell disease

This 4-year-old male presented first with bone crisis at the age of 2 months in association with anemia that

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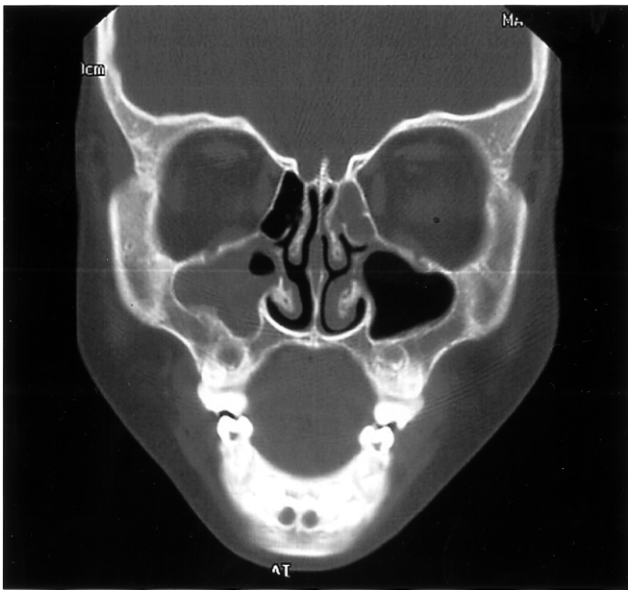

Fig. 1. CT scan of sinuses and adenoid showing complete opacification of the left ethmoid and the right maxillary sinuses.

needed multiple blood transfusion and hematuria. At the age of two years he was presented with a chest infection, hypokalemic metabolic alkalosis. Sweat chloride test was positive of 106 and 104. Family history was significant in that both parents are first cousins. An uncle and an aunt have SS disease and required repeated blood transfusions. One niece died at 2 years of age with cystic fibrosis (CF) in a local hospital and another niece diagnosed at the age of 6 months with CF and SS disease but refused to come for evaluation to our center. Investigation showed: Hemoglobin electrophoresis was positive (+ve) for sickle cell disease. Hb A1 level 3.3 (N 96–98%), HbF 22.9 (N 0.0–1.0%), Hb A2 0.0 (N 2.2–3.7%), and Hb S 64.8 (N 0.0–0.0). At 2.5 years, he developed symptoms of upper airway obstruction as loud snoring and obstructive apnea. Lateral neck X-ray showed a large adenoid that is obstructing the nasal passage. The patient had Tonsillectomy and adenoidectomy with marked improvement of the clinical picture. Random urine sample showed a picture of hyper calciurea and hyper uricosurea. Calcium level 0.78 mmol/l, uric acid 2.89 mmol/l, Creatinine 6 mmol/l, and oxalate level 0.45 mmol/l. Nasopharyngeal aspirate grew *Staphylococcus aureus* that is resistant to Penicillin, but sensitive to Augmentin, Cefzolin and Cloxacillin. Chest X-ray (C-X ray) showed mild peribronchial wall thickening, otherwise within normal limit. Barium swallow showed intermittent Gastr-esophageal reflux (GER). Computerized (CT) scan of sinuses (Fig. 1) showed opacities involve right maxillary and left ethmoid sinuses. MBG scan of 99m technetium DMSA scan showed normal outline in all aspects of the renal cortex bilaterally. Treatment of his CF disease was similar to any other patient with the same disease as Pancreatic enzymes, multivitamins, Bacterim prophylaxis, Folic acid Hydrochlorothiazide as diuretics to improve hyperuricosurea and inhaled Salbutamol and Becotide 2 times/day. He showed marked improvement in his symptoms with normal growth and development. Regarding his SS disease, he received regular blood transfusion regimen at a local hospital. Stem cell transplantation was considered to be done in the near future once the program in our center is well established as it was still in its initial stages. Analysis of CFTR mutation, showed a novel Arab mutation H139L in exon 4 in the first allele and S549R mutation in exon 11 in the other allele (compound heterozygous) (Fig. 2) [9,10]. HbS mutation in β-globin gene was detected by digestion with *Dde I* restriction enzyme; our case showed homzygosity for the mutation E6V that causes HbS [11]. Screening for both parents with hemoglobin electrophoresis showed both of them had sickle cell trait.

Sickle cell anaemia and cystic fibrosis are diseases with autosomal recessive inheritance. Since the β-globin gene cluster is on chromosome 11 and the CFTR gene is located on chromosome 7, there is little likelihood of linked inheritance under normal circumstances. The chances of these diseases coexisting in our patient would be in the range of $(1/4243)\times(1/137)=1/581291$ live births, i.e. it will be a rare combination. This calculation assumes both diseases are inherited in an autosomal recessive pattern in which both parents contribute an abnormal allele for sickle cell disease and cystic fibrosis to the child. However, such a case will be more frequent in our population than others because of large family sizes, consanguineous marriages and common ancestor(s). Hypoxia in patients with both cystic fibrosis and sickle cell anaemia may pose a special management problem especially in patients with bronchiectasis and chronic pulmonary infection [12]; they may become severely and chronically hypoxic. It will increase the likelihood of irreversible sickling [12]. A patient with both diseases is more likely to develop hypoxia at an earlier age and may have more severe pulmonary disease than a patient with either disease alone. For these reasons, it would seem reasonable to consider a chronic transfusion regimen and chelation for patients with both disorders [12].

There have been four cases with the combination of SS disease and CF were described [13–15], but only our case was proved by genetic mutational detection of both diseases. All 4 cases required chronic transfusion regimen and had recurrent admissions for chest infection. Only one of them [14] required home oxygen. In our patient, it is early to evaluate his prognosis, as he is still 4 years old.

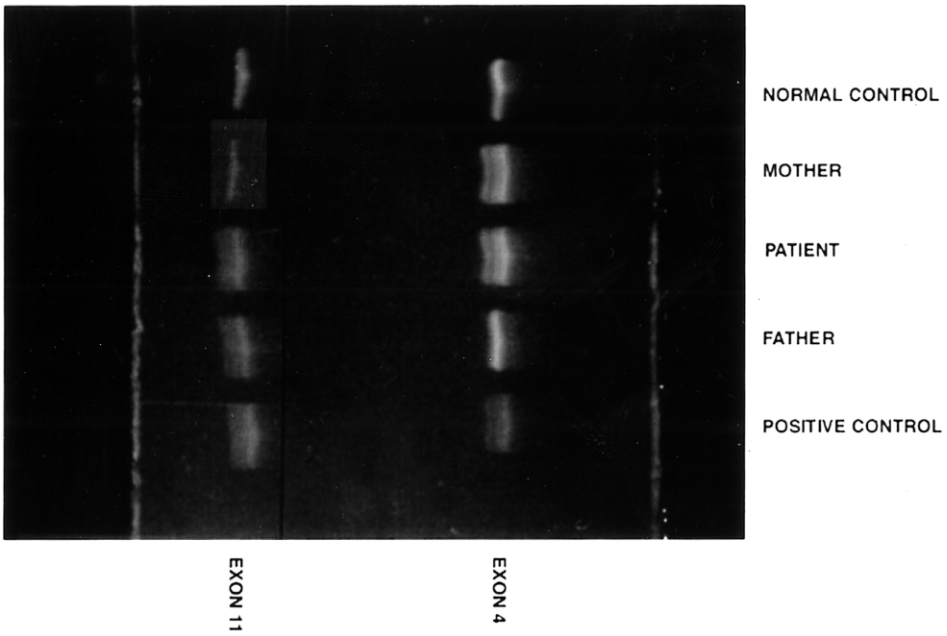

Fig. 2. Mutation detection enhancement (MDE) gel showing similar heteroduplex band in the mother and the patient in exon 4, and another similar heteroduplex band in the father and the patient in exon 11 of CFTR gene.

5. Cystic fibrosis and congenital adrenal hyperplasia (CAH)

The patient presented at 2 years and 6 months of age with a history of (H/O) failure to thrive (FTT), repeated chest infection, chronic cough and vomiting, no H/O diarrhea, or increase in sweating. Both parents are first cousins, one sister died at 3 months of age with chest infection. On examination, she was found to have ambiguous genitalia, but no skin pigmentation. Investigations showed sweat chloride tests on two occasions 130 and 140 mmol/l. Serum electrolytes were normal. Chromosomal study showed normal female karyotype with 46 XX. 17 OH progesterone level was elevated 4.9 ($N=0.3–2.5$ nmol/l), dehydroepiandrsterone sulfate (DEHAS) was low 0.47 ($N=0.7–11$ μmol/l), and random serum cortisol was normal 384 ($N=85–460$ nmol/l). CFTR was carried out as described previously [9], and was found to have homozygous $711+1G\rightarrow A$ in intron 5. She was started on pancreatic enzymes, fat-soluble vitamins, and hydrocortisone replacement. She was maintained on Cotrimoxazole prophylaxis and inhaled Gentamicin. She had initial improvement but later she needed 10 admissions within a 2-year period for respiratory infection and vomiting. Her respiratory culture grew mucoid *Pseudomonas aeruginosa*, which was resistant to Gentamicin. She underwent Nissen fundal plication and gastrostomy tube insertion. Her chest X-ray showed progressive bronchiectasis that involved the right upper lobe, right middle lobe and lingual. She continued to lose weight and appetite in spite of gastrostomy feeding with high caloric regimen and became oxygen dependent at home. She was not compliant to treatment. She was admitted to a local hospital at 6 years old with severe chest infection and expired soon after admission.

CAH is the commonest adrenal disorder in infancy and childhood [16]. The incidence in the Gulf area was estimated to be 1:7000 [17]. It is an autosomal recessive disorder, which results from a deficiency in one or other of the enzymes of cortisol biosynthesis. In approximately 95% of cases, 21-hydroxylation is impaired in the zona fasciculata of the adrenal cortex so that 17-hydroxyprogesterone is not converted to 11-deoxycortisol [16]. This causes excessive production of androgens, resulting in virilization. The gene was mapped to be in chromosome 6, Locus 6p21.3 [16]. The incidence of both associations in the same patient: CF and CAH would be estimated to be $1:4243\times7000=1:29701000$. Both diseases present with FTT, poor feeding, vomiting and dehydration. Factors that could explain the progressive lung disease may include persistent vomiting (due to CAH or recurrent GER), chronic mucoid *Pseudomonas* colonization, and early development of resistance to Gentamycin, non-compliance to treatment and chest physiotherapy. It is difficult to evaluate the role of CAH since the patient was already on treatment. Treatment of this patient for her CF disease was similar to any patient with the same disease except for the small dose of hydrocortisone, which was added as treatment for her CAH. The patient didn't need any emergency treatment for dehydration or electrolyte loss in spite of progressive lung deterioration.

CAH may have affected the progression of her disease due to recurrent vomiting and aspiration with progressive lung damage.

6. Cystic fibrosis and Ehler's Danlos syndrome (ED)

The patient presented at 10 years with H/O recurrent chest infection since the age of one month and had multiple admissions for pneumonia. He developed three attacks of pneumothoraces and one of them needing ventilation for 3 weeks. Cystic fibrosis was confirmed by high sweat chloride tests of 96 and 114 mmol/l. He had pectus carinatum, severe clubbing, hyper mobility of all joints and elastic skin. His mother and two paternal aunts had hype mobile joints, but the father was negative. PFT showed severe obstructive lung disease and air trapping. Chest X-ray showed bilateral extensive Bronchiectasis. Sputum culture grew mucoid *Pseudomonas*, which was resistant to Ceftazidime and Gentamicin. The patient had progressive deterioration with multiple admissions for chest infection and became oxygen dependant within one year after diagnosis. The patient died shortly thereafter from respiratory failure.

ED syndrome is a group of related heritable disorders of connective tissue disease affecting skin, ligaments, joints, blood vessels and internal organs [18]. It is characterized with hyper extensibility, articular hypermobility and tissue fragility. There are 10 types described based on clinical, genetic and biochemical finding [18]. Our patient had type 3, which is the hypermobility of an autosomal dominant inheritance. This disease has affected his progressive course of CF due to abnormal elasticity of the lung that causes progressive alveolar distension and subsequent pneumothoraces (abnormal collagen fibrils structure of the lung due to deficiency of lysyl hydroxylase enzyme) [20], which is a known effect of this disease [19]. Review of the literature has shown only one case report of similar combination but has the kyphoscoliosis type or type 6 of the international classification [20], which is an autosomal recessive inheritance. The disease involved two sisters of consanquineous Turkish parents. Both patients had muscular hyptonia at birth, delayed development, progressive kyphoscoliosis, joint dislocation, Marfanoid habitus, hypertrophic and atrophic scars and osteopenia. Both patients died of lung disease.

ED may have affected the course of the disease in our patient due to recurrent pneumothoraces and chest infection, which are a known complication of this disease due to elasticity of the lung. The combination of CF and ED had a compound effect on the progression of lung disease and early death.

6.1. Other disease association with CF

There were other combinations of disease with CF that were detected in our population: One sister 13 years old and a brother 5 years old were diagnosed with insulin dependant diabetes mellitus (IDDM) early in life and later with CF [21]. Another association was twins with cardiac anomalies and CF was identified [22]. One of the twins had atrial septal defect, which was closed surgically. The other twin had ventricular septal defect, which was closed spontaneously. Both twins had an identical clinical picture later in the disease.

7. Summary

Combination of cystic fibrosis and other inherited diseases such as: sickle cell disease, insulin dependant diabetes mellitus, congenital adrenal hyperplasia, cardiac anomalies and Ehlers–Danlos syndrome have affected the course of the disease in most of the patients mentioned in our study. Other factors such as compliance to treatment and CFTR mutations may have played a role in the course of the disease progression, but was difficult to measure.

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